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MYOCARDIAL METABOLISM

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The Conduction and Cardiac Sympathetic Systems: Metabolic Aspects

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Compared with the myocardium, glycolytic enzymes are reduced by 50% and mitochondrial enzymes and space by 70% in the conduction system of the calf heart. In addition, on the basis of adenosine triphosphate activities energy demands are reduced by more than 50%; this is in parallel with the reduction in myofibrillar space. The increased tolerance of the conduction system against ischemia can be explained by a reduction of energy demands and a higher proportion of (anaerobic) glycolytic as opposed to aerobic mitochondrial energy production. Among the structures of the conduction system, the sinoatrial and atrioventricular nodes are markedly susceptible to hypoxia in contrast to atrial conduction and ventricular conduction by way of the His-Purkinje system.

In the isolated perfused rat heart, an increased net release of noradrenaline during the first 10 minutes of ischemia is only noted after sympathetic stimulation. During this phase, catecholamine overflow is limited by the activity of the neuronal reuptake. At a later second phase, from 15 to 40 minutes after the onset of ischemia, the mechanism of noradrenaline net release is carrier-mediated efflux inhibited by neuronal uptake blocking agents. During the third phase of ischemia, after about 40 minutes, spontaneous noradrenaline release is greatly augmented, probably as a result of leakage caused by membrane damage.

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In most patients, sudden cardiac death is caused by ventricular tachyarrhythmias that are based on inhomogeneity of excitable cardiac tissue, the most common cause being ischemia. This inhomogeneity can be attributed to different phases of ischemic damage either of the myocardium or the conduction system, or both. Furthermore, the metabolic changes may be modulated by local factors such as sympathetic discharge. The changes occurring in the energy metabolism of the working myocardium during ischemia have been discussed previously (1). Little information, however, is available regarding the metabolic changes of other cardiac structures such as the conduction and the sympathoneuronal system.

Conduction System

Energy production and demands. After staining with fluorescein, the right and left main bundle of His of the calf heart can be visualized in the ultraviolet light and then easily isolated (2). By determination of enzyme activities in homogenates of myocardium and of the conduction system, energy metabolism has been evaluated (2). In addition, with the use of light microscopic and electron microscopic techniques, the myofibrillar and mitochondrial space in the His-Purkinje system and myocardium has been determined morphometrically (3).

Glycolytic energy production. In Figure 1, enzyme distribution patterns are shown for glycolytic and other cytoplasmic enzymes. Glycolytic enzymes are present in the conduction system in only about half the activity as compared with the myocardium. Because glycolytic flux depends on the instantaneous activities of regulatory enzymes, glycolytic flux is reduced in the conduction system to the same extent.

Mitochondrial energy production. Aerobic mitochondrial energy production is also reduced in the conduction system (to about 30%). This also applies to the mitochondrial activity of bilocular enzymes. The contents of cytochromes (Cyt a and Cyt c) and mitochondrial space are likewise greatly reduced in the conduction system (Fig. 2). Because mitochondrial space, mitochondrial enzyme activ-

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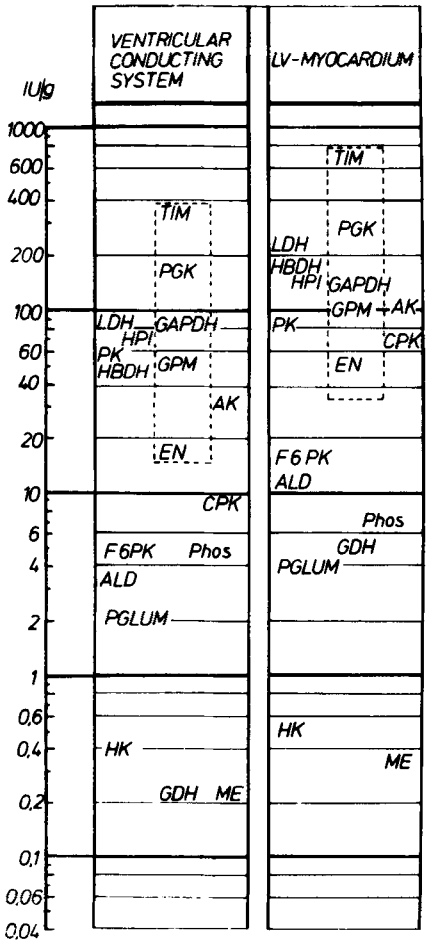

Figure 1. Distribution pattern of cytoplasmic enzymes in the conduction system and the myocardium of the calf's heart. AK = adenylate kinase (2.7.4.3.); ALD = fructose-1,6-diphosphate-aldolase (4.1.2.b); CK = creatine kinase (2.7.3.2.); EN = enolase (4.2.1.11.); F6PK = fructose-6-phosphate-kinase = phospho-fructo-kinase (2.7.1.11.); GAPDH = glyceraldehydephosphate-dehydrogenase (1.2.1.12.); GDH = L-glycerol-3-phosphate: NAD oxidoreductase = glycerine-1-phosphate-dehydrogenase (1.1.1 8.); GPM = phosphoglyceromutase (2.7.5.3.); HBDH = alpha-hydroxybutyratedehydrogenase = LDH-isoenzyme I; HK = hexokinase (2.7.1.1.); HPI = glucosephosphate-isomerase (5.3.1.9.); LDH = lactic dehydrogenase (1.1.1.28.); ME = malate dehydrogenase (decarboxylating) = malic enzyme (1.1.1.40.); PGK = phosphoglycerate kinase (2.7.2.3.); PGLUM = phosphogluco-mutase (2.7.5.1.); Phos = phosphorylase a + b (2.4.1.1.); PK = pyruvate kinase (2.7.1.40.); TIM = triosephosphate isomerase (5.3.1.1.). Numbers in parentheses indicate classifications according to enzyme commission's numbering system.

ities and the amount of cytochromes are reduced in the conduction system to the same extent, the contents of cytochromes and enzymes per volume mitochondria are almost identical in the conduction system and myocardium.

Energy demands. In the conduction system, energy demands are also reduced. Specific potassium-sodium–adenosine triphosphatase (ATPase) activity as well as calcium- and magnesium-induced adenosine triphosphate (ATP) lysis are reduced in the conduction system by more than 50%. In addition, myofibrillar space is reduced (Fig. 3).

The following conclusions may be made: 1) energy production in the conduction system is reduced; 2) energy demands are also reduced; and 3) the ratio of anaerobic glycolytic to aerobic mitochondrial metabolism favors glycolysis in the conduction system. The metabolic data explain that the conduction system can tolerate a longer period of ischemia than can the myocardium (5) because of a higher proportion of glycolysis on total energy production and a decrease in energy demands.

The SA and AV nodes. To study metabolic characteristics of the sinoatrial (SA) and atrioventricular (AV) nodes, the effects of severe hypoxia and inhibitors of glycolysis were investigated in the isolated superperfused preparation of the rabbit heart (6) and a right ventricular preparation of the canine heart (7). Whereas sinus rate and AV conduction, both dependent on slow inward current, are markedly decreased under hypoxic conditions, atrial and ventricular conduction by way of the His-Purkinje system are virtually unchanged. In all hypoxic experiments, the addition of jodoacetate or desoxyglucose, or both, to block glycolysis results in sinus arrest and atrial and AV nodal conduction block (Fig. 4). Under aerobic conditions, however, inhibition of glycolysis produced none of these effects. The data reveal marked differences in susceptibility to hypoxia of different structures of the condition system.

Sympathoneuronal System

The occurrence of myocardial necrosis (8) and ventricular tachyarrhythmias (9), has been related to high local concentrations of noraderenaline during ischemia. The positive results of secondary prevention beta-blocking trials after myocardial infarction may support this concept. Cardiac catecholamine release during ischemia was, therefore, investigated in the isolated perfused rat heart preparation (10).

Catecholamine release during ischemia. Without sympathetic stimulation, no increase in net noradrenaline release can be detected in periods of ischemia ranging up to 10 minutes. After prolongation of the ischemic period beyond 10 minutes, increasing amounts of noradrenaline are released. After 60 minutes of ischemia, the cardiac catecholamine stores are almost depleted. The amount of noradrenaline in the venous effluent during reperfusion, in principle, decreases with time, indicating a simple washout process (10). This is also the case for adrenaline and deaminated metabolites such as 3,4 dihydroxy-phenyl-ethylen-glycol.

Effect of an inhibitor of neuronal reuptake. Catecholamine net release was further investigated after

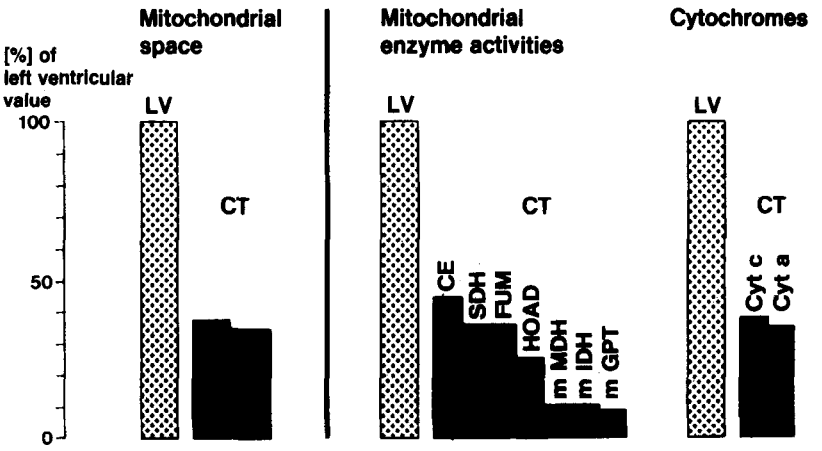

Figure 2. Aerobic energy production. Activities of mitochondrial enzymes of cytochrome (cyt) contents and of mitochondrial space in the conduction system (CT) expressed as percent (%) of the value obtained in the left ventricular (LV) myocardium. CE = condensing enzyme = citrate synthase (4.1.3.7.); FUM = fumarase (4.2.1.2.); HOAD = beta-hydroxy-acyl-CoA-dyhydrogenase (1.1.1.35.); m = mitochondrial activity of bilocular enzymes; m-IDH = mitochondrial isocitrate-dehydrogenase (1.1.1.42.) = mitochondrial aspartate-aminotransferase (2.6.1.1.); m-MDH = mitochondrial malate-dehydrogenase (1.1.1.37.) Numbers in parentheses indicate classification according to enzyme commission's numbering system.

different phases of ischemia with and without desipramine, an inhibitor of neuronal reuptake, the main inactivation process for catecholamines. Under aerobic control conditions and at the beginning of ischemia, net catecholamine release was either increased or unaffected by the administration of desipramine. After more than 10 minutes of ischemia, however, desipramine reduced cardiac catecholamine release, whereas after 60 mintues it had no effect on cardiac noradrenaline release (Fig. 5). Similar results were obtained with cocaine, another inhibitor of neuronal uptake (11).

Effect of sympathetic stimulation on catecholamine release. To test the effect of sympathetic stimulation on cardiac catecholamine release, the left stellate ganglion was electrically stimulated (12) during an aerobic control period and during a 1 minute ischemic period. Under these conditions, net cardiac catecholamine release was greatly reduced in the ischemic experiments owing to noncontinuous washout and, hence, increased neuronal reuptake. Inhibition of neuronal uptake by desipramine, therefore, greatly increased catecholamine net discharge, especially under ischemic conditions. By extending the ischemic period to 10 minutes, however, this effect of desipramine (increased net catecholamine release) was markedly attenuated. During an ischemic period of 20 minutes, addition of desipramine even further reduced net catecholamine release; this was true in experiments with and without sympathetic stimulation.

Under aerobic conditions, the neuronal uptake blocking agent, desipramine, greatly increased noradrenaline release; the same was true for yohimbine, a presynaptic alpha$_2$-blocking agent. The local anesthetic lidocaine, however, greatly reduced catecholamine release under aerobic conditions, indicating exocytosis of the neurotransmitter. After 20 minutes of ischemia, other mechanisms were operating. Neither yohimbine nor lidocaine affected catecholamine release, whereas the neuronal uptake blocking agent, desipramine, now greatly reduced noradrenaline release.

Summary of data. *During phase 1 of myocardial ischemia*, lasting for approximately 10 minutes under the experimental conditions, spontaneous release of noradrenaline is unaltered compared with aerobic control conditions. However, it is increased by sympathetic stimulation. Because neuronal uptake is still active during phase 1, its inhibition by neuronal uptake and alpha$_2$-blocking agents augments noradrenaline release. On the other hand, local anesthetics greatly inhibit noradrenaline release during this phase. Therefore, the predominant mechanism of noradrenaline re-

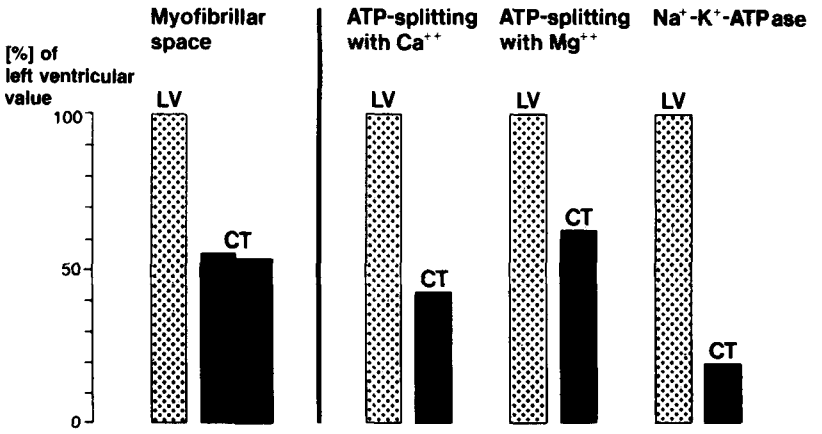

Figure 3. Energy consumption. Sodium (Na^+)-potassium (K^+)–adenosine triphosphatase (ATPase) activity, calcium (Ca^{++})- and magnesium (Mg^{++})-induced adenosine triphosphate (ATP) lysis and myofibrillar space in the conduction system (CT) expressed as percent (%) of the value obtained in the left ventricular (LV) myocardium.

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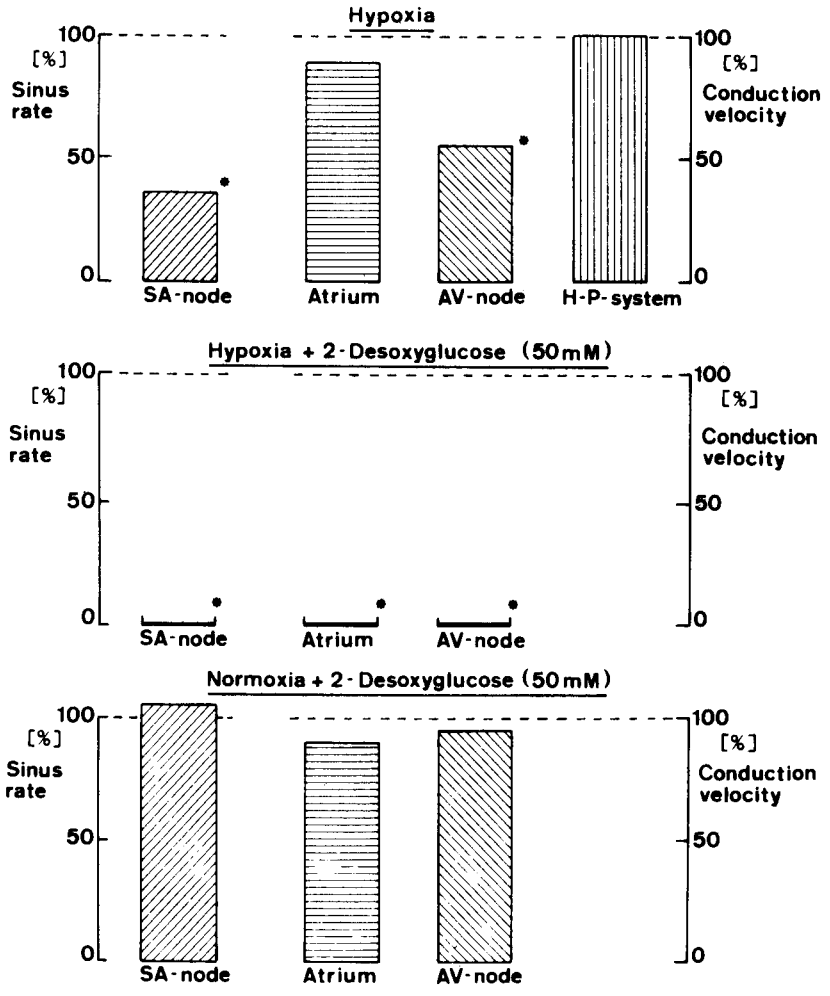

Figure 4. Effect of hypoxia and inhibition of glycolysis on function of conduction system. Sinoatrial (SA) node activity and atrial and atrioventricular (AV) nodal and ventricular conduction by way of the His-Purkinje (H-P) system under normotoxic and hypoxic conditions with and without inhibition of glycolysis with desoxyglucose. The data are given as percent of the value obtained under normotoxic control conditions. *$p < 0.05$.

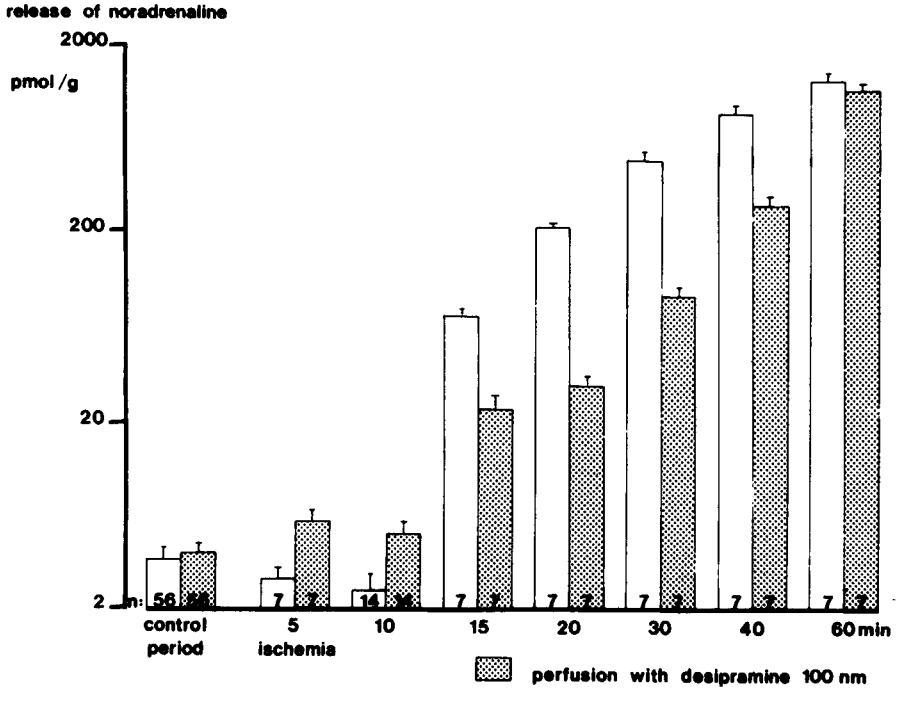

Figure 5. Cardiac noradrenaline release during different phases of ischemia with and without desipramine.

lease during early ischemia can be assumed to be exocytosis similar to that under aerobic control conditions.

During phase 2, lasting for about 15 to 40 minutes of ischemia, spontaneous noradrenaline release is augmented, probably because of impaired neuronal uptake. Under these conditions, net catecholamine release is not affected by sympathetic stimulation. Inhibition of neuronal uptake, however, results in a marked decrease in noradrenaline release. This indicates that the predominant mechanism of noradrenaline release is carrier-mediated efflux.

During phase 3, an ischemic period of at least 40 minutes, spontaneous noradrenaline release is greatly augmented. It is not influenced by neuronal uptake blocking agents; therefore, leakage caused by membrane damage can be assumed to be the predominant release process.

Conclusions. Metabolic inhomogeneity of cardiac tissue during ischemia can be attributed, apart from focal damage of myocardium, to differences in energy metabolism of the conduction system. Ischemic damage and electrical abnormalities are further modulated by local sympathetic activity, which in the ischemic heart is mainly determined by local factors such as catecholamine release and inactivation processes.

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